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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/225,080	01/04/1999	JANICE AU-YOUNG	PF-0066-2-DI	2905

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	18

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/225,080	Au-Young
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *13, 17, and 19-42* is/are pending in the application.

4a) Of the above, claim(s) *13, 17, and 19-38* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *39-42* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. After review and reconsideration the finality of the Office action of Paper No. 12, mailed July 31, 2001, is withdrawn.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. Claims 13, 17, 19-38 remain withdrawn from considration. Claims 39-42 are under consideration.

New Grounds of Rejection

4. The rejection of claims 39-42 under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantion and credible asserted utility or a well-established utility is reapplied for the reasons of record stated in the Office action of Paper No. 10, mailed Feb 6, 2001.

Claims 39-42 are drawn to purified polypeptides comprising SEQ ID NO:2, amino acids having 90% identity to SEQ ID NO:2, wherein said amino acid sequence are expressed on the surface of stem cells, biologically active fragments of SEQ ID NO:2 wherein said fragment are expressed on the surface of stem cells , immunogenic fragments comprising 5 contigous amino acids of SEQ ID NO:2 wherein said immunogenic fragment is capable of generating an antibody that binds to SEQ ID NO:2; and pharmaceutical compositions thereof. The disclosed utilities for the SCAH-2 polypeptide comprising the amino acid sequence of SEQ ID NO:2 or biologically active fragments, immunogenic fragments, and pharmaceutical compositions thereof include the

prevention and treatment of diseases associated with expression of SCAH-2, production of and screening of agonists, antibodies and antagonists that specifically bind to SCAH-2. However, neither the specification nor any art of record demonstrates a correlation between the overexpression of SCAH-2 or lack thereof and the presence of a pathophysiological disease state. Further asserted utilities for SCAH-2, such as production of and screening of agonists, antibodies and antagonists apply to many unrelated polypeptide structures sequences and therefore cannot be considered to be specific to SCAH-2. Additional disclosed uses for SCAH-2 include therapy and diagnosis of conditions and diseases associated with the expression of SCAH-2. The function of SCAH-2 is based on the observation that SCAH-2, (SEQ ID NO:2) has chemical and structural homology to known stem-cell antigens as exemplified in Figure 3, and functional similarities among Ly-6 family proteins particular SCAH-2 and chicken stem cell antigen-2 share 27% identity. However, it is clear that, although there is a 27% identity between SCAH-2 and chicken stem cell antigen-2 there is a 73% dissimilarity between said polypeptides and the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach

that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with 73% dissimilarity, to chicken stem cell antigen-2, the function of the SEQ ID NO:2 polypeptide could not be predicted, nor would it be expected to be the same as that of chicken stem-cell antigen-2. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is

highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein

function as taught by Bork, with a 73% dissimilarity, to chicken stem-cell antigen, the function of the SEQ ID NO:2 polypeptide could not be anticipated. Further, even if the polypeptide of SEQ ID NO:2 is a stem cell antigen, neither the specification nor any art of record demonstrates a real world utility for the SEQ ID NO:2 polypeptide, beyond use as an experimental substrate. Furthermore, the specification provides no teachings regarding the organs or tissue types which would harbor said stems cells, thereofor one of skill in the art would not known where to look for said stem cells. The specification teaches that the polynucleotide of SEQ ID NO:4 were isolated from a cDNA library from a single human leukemia cell line and cancerous bladder tissue isolated from a single individual. However, if the SCAH-2 peptide is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed both in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). The specification fails to provide objective evidence that the polynucleitde encoding SEQ ID NO:2 are not expressed in non-cancerous bladder tissue or in normal henatopoietic cells. This type of evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder and the lack of any correlation

between the claimed polynucleotide or the encoded protein with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. Because the claimed invention is not supported by a substantial specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

5. Applicant has provided exhibit A to demonstrate that SEQ ID NO:2 is identical to Prostate Stem Cell Antigen. Applicant has also provided the reference by Reiter et al, "Prostate stem cell antigen: A cell surface marker overexpressed in prostate cancer" in an attempt to obviate the rejection under 35 U.S.C. 112. However, this has no bearing on the instant application which did not disclose the polypeptide of SEQ ID NO:2, the polynucleotides encoding said polypeptide obtained from a bladder tumor library, as a prostate stem cell antigen but The specification teaches that the simultaneous administration of Ly-6, recombinant SCAH-1 and recombinant SCAH-2 is observed to decrease or destroy the activation of natural killer cells, thus preventing or diminish the lysis of tumor cells by said natural killer cells. The specification does not provide a description of SCAH-2 as a prostate stem cell antigen useful for the diagnosis

of prostat cancer. The reference by Reiter et al represents information that was not available at the time of the instant invention, as the specification does not discuss SEQ ID NO:2 as a prostate stem cell antigen or the use of SEQ ID NO:2 in a diagnostic or therapeutic method. Furthermore, developments occurring after the filing date, i.e. identification of SEQ ID NO:2 as a prostate specific antigen, are of no consequence regarding what one of skill in the art believed as of the filing date the rejections stand. See In re Wright, 27USPQ 1510, 1514 (Fed. Cir. 1993). Furthermore, the instant specification must assert the a specific, substantial and credible utility at the time of filing. The instant specification did not identify SCAH-2 (SEQ ID NO:2) as a prostate specific stem cell useful for the diagnoisis and therapy of prostate cancer. The M.P.E.P.(715.07) states that a utility must be known before reduction to practice can occur (In re Wilkinson, 304 F.2d 673, 134 USPQ 171 (CCPA 1962). As the instant specification was lacking a specific, substantial and credible asserted utility at the time of filing, proof of a specific, substantial and credible utility after the filing date has no bearing on the instant rejection.

6. Claim 39-42 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

In the event that Applicants might be able to overcome the 35 USC 101 rejection above, the specification would still be enabling only for claims limited to polypeptides comprising SEQ

ID NO:2, because the specification does not reasonably provide enablement for amino acid sequences having 90% sequence identity to SEQ ID NO:2, wherein the sequences are expressed on the surface of stem cells, biologically active fragments of SEQ ID NO:2, wherein said fragments are expressed on the surface of stem cells or immunogenic fragments of SEQ ID NO:2, wherein said immunogenic fragments comprsie at least 5 contiguous amino acids of SEQ ID NO:2 and are capable of generating an antibody that specifically binds to the polypeptide of SEQ ID NO: or polypeptide variants having at least 90% sequence identity to SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

(A)As drawn to a polynucleotide comprising an amino acid sequence having at least 90% sequence identity to SEQ ID NO:2

Claims 39 and 42 are drawn in part to polypeptides comprising an amino acid sequence having at least 90% sequence identity to SEQ ID NO:2 wherein the amino acid sequence is expressed on the surface of stem cells. The specification discusses the full length SCAH-2 (SEQ ID NO:2) as being a stem cell antigen or as functioning to inhibit the activation of natural killer cells. However, the specification does not identify variants of SEQ ID NO:2 that would be expressed on the surface of stem cells, or the organs or tissues which would have said stem cells, such as prostate tissue or bone marrow. As the specification does not provide a written description of the amino acid sequences of the claimed variants to SEQ ID NO:2 that are exposed on the cell surface, one of skill in the art could not use the invention as one of skill in the art

would need to where to look for said stem cells, and the specification provides no teachings as to know the organ or tissues harboring said stem cells in order to isolate said cells and determin the sequence of the variant polypeptide.

Due to these reasons, one of skill in the art would be forced into undue experimentation without reasonable expectation of success in order to practice the invention as claimed.

(B)As drawn to biologically active fragments of SEQ ID NO:2

Claims 39-42 are drawn in part to polypeptides comprising biologically-active fragments of SEQ ID NO:2, wherein the biologically active fragment is expressed on the surface of stem cells. Clearly, since the specification has not taught how to the polypeptides comprising SEQ ID NO:2, the specification has not enabled the scope of claims drawn to polypeptides comprising biologically-active fragments of SEQ ID NO:2. The specification discusses the full length SCAH-2 (SEQ ID NO:2) as being a stem cell antigen or as functioning to inhibit the activation of natural killer cells. However, the specification does not identify a portion of SEQ ID NO:2 is expressed on the surface of stem cells, or specific stem cells that would have said fragment on the cell surface, such as prostate, or henatopoietic stem cells. As the specification does not provide a written description of the portion of SEQ ID NO:2 that is exposed on the cell surface, one of skill in the art could not use the invention as one of skill in the art would need to known where to look for said stem cells, and the specification provides no teachings as to the organ or tissues harboring said stem cells in order to isolate said cells and determin the sequence of the expressed fragment. Due to these reasons, one of skill in the art would be forced into undue

experimentation without reasonable expectation of success in order to practice the invention as claimed.

(C)As drawn to immunogenic fragments of SEQ ID NO:2

Claims 39 and 41 are drawn in part to polypeptides comprising immunogenic fragments of SEQ ID NO:2, wherein said fragment is capable of generating an antibody that binds to SEQ ID NO:2. Clearly, since the specification has not taught how to the polypeptides comprising SEQ ID NO:2, the specification has not enabled the scope of claims drawn to polypeptides comprising immunogenic fragments of SEQ ID NO:2. The specification does not list or give examples of any fragments of SEQ ID NO:2 that were used to raise an antibody that would bind to SEQ ID NO:2 The specification states that numerous regions of the polypeptide may induce the production of antibodies but does not teach any examples of such. Paul (Fundamental Immunology, 3rd Edition, pg. 251, column 1, lines 11-12) states that immunogenicity is limited by self-tolerance, and that the repertoire of potential antigenic sites in a given polypeptide is a specific for the host organism. Klein ("Self-nonself discrimination, histoincompatibility, and the concept of immunology", Immunogenetics, 1999, Vol. 50, No. 3-4,pp. 116-123) teaches that the property of immunogenicity for a polypeptide is based upon the recognition of said polypeptide as a "non-self" polypeptide. Ristori et al (FASEB, 2000, Vol. 14, No. 3, pp. 431-438) have disclosed that the discrimination between self and non-self proteins do not rely on simple qualitative features of the amino acid sequences in question, and that foreign, "non-self" peptides, known not to be present in humans, can mimic "self" antigens and thus can be tolerated

(non-immunogenic) within the host. Therefore, it would be difficult to predict what an immunogenic fragment would consist of having only the amino acid sequence of SEQ ID NO:2. Paul also teaches (supra, pg. 249, column 2, lines 10-13) that to determine the immunogenicity of certain regions of a protein, knowledge of the three dimensional structure of the protein is required to determine which polypeptides in a given protein would be accessible on the surface of the protein in order for the putative antigenic determinant to be bound by the antibody. In addition, Paul states that mobility of the putative antigenic determinant within the native protein structure is also a determining factor for the binding of the antigenic determinant to an antibody. Paul points out (supra, pg. 250, lines 4-8) that "Measurement of the mobility in the native proteins largely dependent on the availability of a high resolution crystal structure, so its applicability is limited to only a small subset of proteins." The determination of an immunogenic fragment is clearly a non-trivial enterprise, and without further guidance from the specification on known sequences of the SEQ ID NO:2 polypeptide which have been determined to be immunogenic fragments in a specific organism, it would require undue experimentation for one of skill in the art to make and use the invention as claimed.

7. Claims 39-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39 is rendere vague and indefinite in the recitation of "biologically active fragments". The specification defines biolgoically active on page 5, lines 1-2 as having structual, regulator or biochemical functions of the naturally occuring SCAH. However, there is no description of what constitutes these structual, regulatory orbiochemical functions of the natrually occurring SCAH. Therefore, the metes and bound of claim 39(c) cannot be determined.

8. The rejection of claims 39 under 35 U.S.C. 102(b) as being anticipated by any of Wilkie et al (Genomics, 1993) or Wray et al (Gene 1993) or Burton (Nature, 1993) or Gama et al (Mol. Microbiol., 1992) or Birkeland (Can J. Microbiol., 1994) or Arendt et al (Appl. Environ. Microbiol., 1994) is withdrawn.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

July 15, 2002

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